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BOGGLER, AN INHERITED ABNORMALITY OF THE DEERMOUSE (PEROMYSCUS MANICULATUS), CHARACTERIZED BY A TREMOR AND A STAGGERING GAIT*

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CONTENTS

Introduction 1
  Acknowledgments 3
Method of Testing 3
Description 4
Association between Tremor and Staggering Gait. 6
Convulsions in Boggler Strain 8
Variability in Behavior 9
  Variability among Bogglers 9
  Variability among Nonbogglers. 13
  Criteria for the Classification of Bogglers and Nonbogglers 13
Fertility and Viability. 14
Inheritance 16
Linkage Tests with Hairless and with Brown-tip 19
Comparison with Other Inherited Abnormalities of Behavior. 21
Summary 23
Literature Cited 24

INTRODUCTION

SEVERAL adult individuals of the brown-tip buff and brown-tip gray strains of Peromyscus maniculatus blandus were noted by W. Frank Blair in 1943 to exhibit a pronounced tremor and to walk with a staggering gait. Because of the awkwardness it produces, the character is termed " boggler." The affected mice are designated " bogglers," and the exhibition of the symptoms is called " boggling."

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The first 13 mice identified as bogglers were scattered among eight sibships. They were four to five generations removed by the shortest line of descent from their field-caught ancestors. Although none was detected, bogglers may have been present in one or more of the earlier generations. The mice of the first three laboratory-bred generations were never checked especially for peculiarities of behavior and such examinations as they were given were usually made when the animals were young. Inasmuch as the boggler character is strongly expressed only in adults, its presence in early generations may have eluded notice.

At the time that boggling was first recognized its frequency in the brown-tip strains was not ascertained. Four years after the discovery of the abnormality the behavior of all mice in a subline derived exclusively from the brown-tip strains was checked and three years after that all mice then existent in the strains of brown-tip blandus were examined. At both examinations about one-third of the animals which had reached at least 16 months of age when observed, exhibited a tremor or a stagger or both. On the two inspections 58 mice of the brown-tip strains of P. m. blandus, in which no selection for any abnormality of behavior had ever been practiced, were identified as bogglers.

Every boggler which has been discovered is related through both parents to a pair of animals in the first cage-bred generation of a stock of P. m. blandus that is descended from mice trapped by W. Frank Blair in 1938 near Tularosa, Otero County, New Mexico. This pair and their ascendants, which include four field-caught animals, are the only ancestors shared by all bogglers. One affected mouse derived all of its genes from the two progenitors in the first cage-bred generation. At least one of the two ancestors in the first generation, therefore, must have transmitted a boggler gene. In order to account for all of the observed bogglers it is necessary to assume that at least two individuals of the second cage-bred generation transmitted the boggler gene. If the mutation to boggler arose in the laboratory, then, it must have occurred no later than the first cage-bred generation. But it is quite likely that the mutation had an earlier origin and that the boggler gene was present in the wild population. The four field-caught animals which are common ancestors of all bogglers are also the ancestors of all brown-tip mice of the subspecies P. m. blandus (Blair, 1947). The four trapped individuals may have carried among them not only a gene for brown-tip but a gene for boggler as well.

To establish a strain of bogglers the affected mice from the brown-tip strain were mated to each other and to nonbogglers of the brown-tip, yellow, and hairless strains. The offspring from these matings and their descendants constitute the boggler strain. The yellow and hairless individuals which were crossed with bogglers were hybrids of several subspecies of P. maniculatus, but their striking pelage characters are derived from yellow and hairless ancestors of the subspecies P. m. gambeli (Sumner, 1932).

Acknowledgments

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METHOD OF TESTING

Identification of the mice as bogglers or nonbogglers was based upon their behavior while they were being observed singly in an open-topped wooden box, which, on the inside, was approximately 36 inches long by 24 inches wide by 18 inches high. In most of their tests the mice of the boggler strain moved about for only a short time before resting. Their activity could be renewed whenever desired, however, by prodding them gently. Unless boggling was immediately apparent, a mouse was watched over a series of alternate runs and sittings.

A test seldom lasted more than five minutes. An examination usually was not continued after both a strong tremor and a pronounced stagger had been exhibited. Some trials were stopped as soon as either symptom had been conspicuously displayed. In general, mice which seemed completely normal during the first two minutes in the testing box were observed for a shorter time than were ones which appeared slightly but not extremely abnormal during this period.

Some mice of the boggler strain were tested three times at monthly intervals, starting at about a month of age, shortly after they had been separated from their parents. When it became apparent that severity of boggling increased with age, frequent testing in early life was discontinued. Instead, all mice of the boggler strain which had been removed from their parents were observed from time to time regardless of the number of previous checks or of their ratings during preceding tests. Individuals which showed equivocal behavior at a particular observation period were sometimes given additional tests before the entire strain was rechecked. Examinations usually were continued beyond the fifteenth month, unless the animals suffered injuries, became infested with parasites, or were lost either through escape or death.

At each test an attempt was made to indicate roughly the degree of abnormality that was exhibited. The three grades usually employed were " normal, " " probably abnormal, " and " abnormal. " Occasionally, extreme manifestations of tremor or staggering were noted as " markedly abnormal." In general, trembling and staggering gait were rated separately, but some of the early records lumped the displays of either or both into a single category.

Ratings of tremor and stagger were made by four different observers. The criteria of the separate observers inevitably varied, so that their gradings are not strictly comparable. But identifications of the same animals by independent examiners do afford a test of the distinctness in behavior of normal and affected mice. Except where otherwise noted, however, any bias due to difference in observers has been eliminated as a source of error by using only my own ratings.

DESCRIPTION

Weak boggling is not easily distinguishable from normal behavior, for a slight tremor resembles quaking from fright or shivering induced by cold. The boggler's stagger, when mild, does not differ greatly from the sway of a normal mouse which is making an abrupt turn. If the boggler character is well developed, however, the magnitude of the tremors and the extent of the staggering often far exceed the low-grade trembling and swaying that are a part of normal peromyscus behavior. Hence, the following description is based on the behavior of old bogglers which exhibited their abnormality to a pronounced degree.

The tremor frequently involves the entire body, but movements of the head are at times much more noticeable than those of the trunk, limbs, or tail. The direction of motion of the head and trunk during a tremor is usually from side to side, but sometimes the body will bob rapidly up and down or teeter forward and backward. The rate of the tremor was measured by moving a finger from side to side in time with the trembling of the mouse and counting the finger movements over periods of ten seconds. As nearly as could be estimated, the vibrations were in the neighborhood of six per second.

A tremor usually is apparent only when the affected mouse is awake but resting. In some old animals it was detected when they walked slowly. The frequency with which tembling occurs when a mouse is active is uncertain because of the difficulty of perceiving the shaking when other movements also are present. In resting mice the tremor occurs intermittently. Occasionally, some individuals trembled continuously for several minutes, but in the course of this, periods of quivering of greater and lesser violence alternated. Usually, however, a single period of trembling in an animal at rest lasted only about one second. As a rule, if an affected mouse continued to sit quietly, the severity and frequency of its tremors decreased with the passage of time. If, when the tremors subside, the animal moves about, severe tremors may recur soon after it next comes to rest. After several minutes of alternate running and sitting the tremors of successive rest periods become progressively weaker; a prolonged period of inactivity must intervene before severe tremors can be induced again.

When walking, a boggler progresses jerkily and it frequently bumps into walls. The hind quarters sway from side to side and appear to bounce up and down and, as they are flung upward, the head is sometimes forced downward until the nose bumps the ground. In order to study the details of gait, slow-motion pictures of two bogglers and one normal mouse were taken from beneath through a glass plate. While photographed the mouse was confined to a box with a floor seven inches wide by 11.5 inches long. Limitations of space undoubtedly restricted the number of locomotor patterns demonstrated. The order of footfalls, according to the terminology of Howell (1944), was sometimes that of a diagonal walk (left front, right hind, right front, left hind), sometimes that of a transverse gallop (left hind, right hind, left front, right front, or the reverse order), and in one cycle that of a rotogallop (left hind, right hind, right front, left front). Regardless of the sequence of foot movements, the bogglers were usually supported alternately by three and two limbs. Rarely, except when the mouse came to a halt, were all four feet simultaneously on the ground and in no photograph were they all simultaneously off the ground.

The hind limbs work even more vigorously than those of a normal mouse. A hind limb may become so far extended that femur, tibia, and metatarsals seem to form a straight line. This hyperextension probably is responsible for the upward bounce of the hind quarters, which is most apparent when the sequence of footfalls is that characteristic of a gallop. Staggering is more noticeable during the diagonal walk. In many steps as the hind foot is set down the limb rotates sharply. Direction of rotation usually is outward and the leg then exerts its force obliquely back toward the outside, so that the hind quarters are thrown sideways away from the supporting hind foot. With successive steps of the hind feet the hind quarters are pushed first to one side and then to the other. The hind foot is set down beneath the body or only slightly to the side of it, but as the hind quarters are pushed away the foot and leg protrude far to the side of the trunk. Deviation from normal action is greater during the backward thrust of the hind limbs than during their forward swing, for, when the hind foot is lifted, the limb rotates inward to a more normal position and the foot moves forward beneath the body or close to its side.

The staggering gait is obvious only in the hind limbs. Even in severely affected individuals the action of the front limbs is normal or very nearly so. Whether the front limbs are completely unaffected is uncertain, because locomotion in peromyscus probably tests the motor co-ordination more rigorously in the hind limbs, which furnish most of the propulsive force, than in the front limbs, which are primarily supportive in function. An abnormality of the front limbs comparable to that of the hind limbs, therefore, might not be readily detected. Some affected individuals swing their tails vigorously as they walk, occasionally bending them as much as ninety degrees near the base. The tail movements of a mouse which is walking normally, at least under the conditions of the tests, are more restricted.

Severely affected mice lack dexterity in certain operations, but they are able, by persistence, to accomplish the routine tasks of their daily existence with a proficiency that satisfies the relatively undemanding requirements of life in a cage. They are less adept at climbing than normal mice, but are able to gain access to food in containers with openings 2 3/4 inches above the floor of the cage. They are prone to lose their balance, but they right themselves readily after a fall. They do a creditable job of grooming. They dig effectively. The nests which they build are well constructed. The in-co-ordination of the hind limbs is not apparent during all activities. Back somersaults have been executed in good form by bogglers which had a well-developed stagger. Swimming ability seems to be unimpaired.

Insofar as could be determined by watching the response of animals to squeaks, which the observer emitted by inspiring through the mouth while the lower lip was pressed against the teeth, the hearing ability of bogglers does not differ from that of phenotypically normal animals of the boggler strain. When young, both bogglers and related normal animals gave strong ear movements or jerks of the body or both immediately after the sound. Older animals of both phenotypes reacted less violently to the squeaks than did young mice. A few bogglers and one normal animal, all at least 30 months old, failed to show any perceptible response to the sound. Because very little is known of the extent of hearing loss usual among mice of this age class in normal strains of peromyscus, it is impossible to say whether the decline in hearing ability with age in the boggler strain was abnormal in degree, or not.

Like normal mice, bogglers respond to a gentle touch on the back or tail by moving forward, and jump when the floor on which they are standing is jarred. When held too tightly by the tail, they evidence pain by biting. The ability to blink the eyes is retained. Neither the fore limbs or the hind limbs offer abnormal resistance to passive movement.

No defects of either the muscles or skeleton were found to be regularly associated with the abnormal behavior. Bogglers rarely become emaciated. No atrophy of the muscles of the hind limbs could be detected by gross examination. Sections of the biceps femoris stained with hematoxylin and eosin appeared normal. The microscopic examination of muscles was not pursued far enough to completely rule out the possibility that degeneration of some sort may occur in some muscles, but the search carried out yielded only negative findings. No excessive curvature of the feet was detected. Kyphosis was noted in a few very old individuals, but its frequency was not appreciably higher among bogglers than among non-bogglers. A superficial examination of the brains of affected mice revealed no abnormalities. No histological study of the nervous system, however, was made.

ASSOCIATION BETWEEN TREMOR AND STAGGERING GAIT

Both a tremor and a staggering gait were observed in several of the first bogglers to be discovered. In subsequent generations of the brown-tip strain and in the boggler strain, most of the mice have fallen into one of two classes: (1) those which exhibit both a tremor and a stagger and (2) those which display neither symptom. In a few animals only one of the symptoms has been recognized, but failure to note both a tremor and a stagger in them may be a consequence of insufficient observation.

If tremor and staggering gait are determined by genes at different loci, the genes should sometimes separate following crosses of bogglers with unrelated normal animals. In F_2 generations from such crosses, however, among mice at least 16 months old, all but one of 16 mice examined which gave a clear display of one symptom also exhibited the other. Staggering but not a tremor was observed in one individual, but this animal was examined only twice when more than 15 months old. It was not, therefore, tested enough times to prove that a tremor was actually lacking.

To check association between tremor and staggering gait further, all mice of the boggler strain which were available during a certain 12-day period were checked three times for trembling and three times for gait. Trembling and gait were rated on separate days. Ages of the mice were from five to 52 months, and both affected and normal animals were included in the group. Results are given in Table I.

TABLE I

Association between Tremor and Staggering Gait

Highest Grade of Staggering on Three Trials	Highest Grade of Tremor on Three Trials							
	Mice Less Than 16 Months Old				Mice at Least 16 Months Old			
	Normal	Probably Abnormal	Abnormal	Total	Normal	Probably Abnormal	Abnormal	Total
Normal	34	11	1	46	27	2	0	29
Probably Abnormal . .	2	4	9	15	0	1	0	1
Abnormal . . .	0	2	14	16	0	0	16	16
Total. . . .	36	17	24	77	27	3	16	46

Mice which were at least 16 months old when the tests were given could be separated with more certainty into abnormal and normal categories than could younger animals. The ratings for the two age groups, therefore, are presented separately. In the older age group every individual which displayed one symptom clearly expressed the other one strongly. Although the tendency for a mouse to have both symptoms or neither of them is apparent also in the younger age group, there it is partly obscured by the mildness of the symptoms. Subsequent examinations of the mice in the younger age group, given after the disorder had progressed farther, revealed clear expression of both a tremor and a stagger in 25 of the 26 animals originally rated abnormal for either symptom during the 12-day series of tests. One mouse, when last tested at 13 months of age, had a definite stagger but only a slight tremor.

Failure to find any certain instance of a mouse which had one of the two symptoms of the boggler character but lacked the other is good evidence that the gene determining tremor either is identical with that determining the staggering gait or is tightly linked with it. The simpler hypothesis that the two symptoms are different manifestations of the same gene is adopted here.

CONVULSIONS IN BOGGLER STRAIN

Twenty mice of the boggler strain scattered among 14 sibships have been observed to have convulsions. In two of the convulsive individuals the seizures were induced by a jingling of keys and the pattern of attack was similar to that of sound-induced convulsions in a strain of convulsive, whirling peromyscus derived from a stock of P. m. artemisiae from Lyons Ferry, Washington (Dice, 1935; Watson, 1939). The seizures in the other 18 occurred in the absence of key jingling and followed a pattern distinct from that of the sound-induced attacks. This second type of seizure always began soon after the cage of a susceptible mouse had been moved or opened, and it occurred either while the mouse was still in its cage or shortly after it had been transferred to the observation box. Symptoms were opisthotonos, spasmodic movements of the mouth, blinking, beating up and down with the raised forepaws, and rolling or falling onto the side. The two mice which had sound-induced convulsions were five and 20 months old when the seizures were observed. Attacks not induced by sound occurred at ages as early as three months and as late as 38 months. Although frequency of attack varied among individuals, no mouse of the boggler strain which was checked more than once had a seizure every time that it was observed.

Proneness to convulsions has not yet been proved to be part of the - boggler syndrome. Even if a convulsive tendency is an expression of the boggler gene, it has only been revealed in a small proportion of bogglers by the testing procedures employed. Furthermore, although most of the convulsive animals developed a tremor and a staggering gait, not all of them did so. One mouse, which displayed neither a tremor nor a stagger during any of 15 tests when it was more than two years old and which could, therefore, be identified with certainty as a nonboggler, was observed to have three convulsive seizures. From this it seems evident that not all of the convulsions in the boggler strain can be ascribed to the boggler genotype. There remains a possibility that at least two genetically distinct types of convulsions are represented in the boggler strain. Several of the convulsive animals, including the convulsive nonboggler, are the products of outcrosses and both branches of their pedigrees include convulsive individuals. The convulsions in the two ancestral strains have a similar pattern, but they have not been proved to be genetically identical.

Although not all bogglers are convulsive and not all convulsives are bogglers, the following observations suggest that some of the seizures may be related in some way to the boggler syndrome. (1) a few of the convulsive bogglers derive all of their genes from the brown-tip strains of blandus from Tularosa. Unless, in these individuals, the tendency to seizures is nonhereditary, the same strain which furnished the boggler gene must have contributed a gene for convulsive susceptibility. (2) Among bogglers an association apparently exists between convulsive susceptibility and early age of onset of a tremor and a staggering gait (see further discussion in next section). Such a relationship might result either if the susceptibility is a separate character which enhances the action of the boggler gene or if the convulsions are an extreme manifestation of the boggler gene itself. (3) The unit-gene characters jittery (DeOme, 1945), varitint waddler (Cloudman and Bunker, 1945), trembler (Falconer, 1951), and dilute lethal (Russell, 1951; Searle, 1952) in the house mouse (Mus musculus) include in their syndromes both an abnormality of gait and convulsions. The convulsive pattern is similar to that in the boggler strain which is not induced by sound. Although the boggler character differs in important particulars from any of these of the house mouse, the behavior parallel is so close that the occurrence of convulsions in bogglers may not be just a chance combination in the same individual of two unrelated disorders.

VARIABILITY IN BEHAVIOR

Severity of boggling fluctuates from moment to moment in the same individual. Whenever the intervals between observation periods are sufficiently long, a trend toward greater severity of boggling with increasing age becomes obvious. Occasionally although not frequently, under the conditions used for observations, a nonboggler exhibits behavior which is mistaken for boggling. The extent of the variability in behavior among bogglers and nonbogglers and the precautions taken to avoid errors in classification are considered below.

Variability among Bogglers

An approximate indication of the amount of variability in boggling from moment to moment is provided by the length of observation required to identify the symptoms. For 13 mice, all of which had previously exhibited both a tremor and a stagger to a degree which was clearly but not markedly abnormal, the interval from the time the mouse was placed in the observation box until abnormal trembling began, varied from 2 to 230 seconds, with a mean of 72 seconds. To identify a stagger in these same mice, when their gait was examined about an hour later, 6 to 39 seconds were required, with a mean of 21 seconds.

Both frequency and severity of boggling vary directly with age. Mice may give weak displays of boggling which cannot be distinguished with certainty from normal behavior months before they first exhibit a definite tremor or stagger. In some of the tests which immediately follow the first clear expression of the boggler character, an affected individual may appear normal or only slightly abnormal, or it may show either a tremor or a stagger, but not both symptoms, clearly. But as the character develops further, both a tremor and a stagger are expressed strongly at almost every observation period. Because the grading system did not distinguish between slight differences in behavior which was clearly abnormal, it is impossible to be certain whether or not the development of the character ever becomes arrested. The impression gained from examining affected mice from time to time throughout their lives, however, is that the symptoms become increasingly severe, at least up to 54 months, the oldest age at which any boggler was tested. Recovery from boggling has never been known to occur. No mouse of the boggler strain which was rated abnormal on as many as two tests appeared, thereafter, to be consistently normal.

Because the earliest manifestations of the boggler syndrome are not sharply differentiable from normal behavior, the exact age of onset of the character in any individual is uncertain. The earliest age at which boggling has been displayed clearly is 87 days. At earlier ages no behavior which seemed even slightly abnormal was noted; 30 mice, which later proved to be bogglers, were checked when they were two months old and 25 other bogglers were tested at one month of age. The oldest age at which a mouse, which eventually has been identified as a boggler, has failed consistently to exhibit the boggler character clearly when tested several times is fifteen months. Bogglers which failed to show a definite tremor or stagger before they were 16 months old did, however, display mild symptoms at earlier ages.

Individuals, even within the same sibship, differ widely in the age at which their symptoms first become apparent. One mouse which was observed twice when it was five months old, 10 times at seven months, and three times at 10 months of age, displayed a definite tremor on each of the 15 trials and a gait which was unmistakably abnormal on all but two of them. Another mouse of the same sibship did not express the boggler character clearly until it was 16 months old. In fact, it seemed entirely normal on 12 out of 14 tests given when it was between six and 11 months old and during one of three tests at 15 months. Even at 16 months, although it then displayed a tremor clearly on each of four tests, its gait was only slightly abnormal. But at 17 months it had both a distinct tremor and a definite stagger.

Although individuals vary greatly in the age at which they first exhibit their symptoms regularly and clearly, all bogglers so far raised, if they were sufficiently long lived, eventually reached a stage at which they displayed the symptoms during almost every trial. The distribution of grades of behavior at different ages among 69 mice that were obtained from matings of boggler x boggler are presented in Table II. Inasmuch as all offspring from this type of mating are expected to be potential bogglers (see Inheritance, below), all those tested at least once are included in the table, whether or not they were ever seen to display the characteristic symptoms. Mice are listed in the table as " normal" for tests on which ratings for both trembling and gait were normal. They are listed as " abnormal" for tests in which either symptom was rated abnormal. Animals assigned to the " probably abnormal" category are the ones that were rated probably abnormal with respect to either symptom but which revealed neither clearly. Not all of the mice were checked at any one age level. The age at which their behavior was first observed varied from one to 19 months. The number of observations per mouse was from one to 27. Ratings for any mouse which reacted differently at separate times during a single age interval have been divided among the classes according to the proportion of times that the mouse qualified for each of them. For example, a mouse which, between the ages of 7 1/2 and 8 1/2 months, appeared normal twice, doubtful 7 times, and abnormal once, is tabulated as .2 normal, .7 doubtful, and .1 abnormal at eight months of age.

TABLE II

Frequency Distribution of Grades of Boggling According to Age

Age to Nearest Month	Number of Mice			
	Normal	Probably Abnormal	Abnormal	Total Tested
1	19.0	0.0	0.0	19
2	18.0	0.0	0.0	18
3	17.0	1.0	1.0	19
4	8.0	2.0	3.0	13
5	8.0	4.0	1.0	13
6	1.5	0.5	0.0	2
7	7.5	2.0	3.5	13
8	2.8	1.9	5.3	10
9	5.7	6.6	8.7	21
10	1.2	3.0	5.8	10
11	3.5	6.8	3.7	14
12	2.0	3.0	11.0	16
13	0.5	4.5	7.0	12
14	1.0	2.0	8.0	11
15	0.3	3.7	9.0	13
16	0.0	2.0	19.0	21
17	0.0	1.5	15.5	17
18-20	0.0	1.0	13.0	14
21-24	0.0	0.0	11.0	11
25-44	0.0	0.4	23.6	24

As the age of the bogglers tested advanced from two to 16 months the proportion of tests which revealed only normal behavior dropped from 100 per cent to zero. Only three of 10 bogglers checked at eight months exhibited their abnormality on every test at this age, but after five observations at eight months nine of the 10 animals had exhibited at least one symptom during one or more tests. On the average a single test at eight months revealed clearly abnormal behavior in about half of these 10 mice. When more than 15 months old no offspring from matings of boggler x boggler appeared completely normal during any test and most of them were clearly abnormal during every trial.

If more offspring from such matings had been raised and tested or if the number of observations per mouse had been increased, a few individuals in the group might have appeared normal during an occasional test even when as old as 16 months. For the chance of obtaining the observed record of only " abnormal" or " probably abnormal" behavior among 21 bogglers observed once at 16 months would be .025, if the probability of a boggler's appearing normal throughout a test at this age were as high as .161. Among bogglers derived from other types of matings, although a few individuals seemed normal during some examinations when they were more than 15 months old, the proportion of animals which failed to display abnormal behavior on a test after this age was well below 16 per cent. When first tested at 16 months, for example, of 14 bogglers which had at least one phenotypically normal parent, only one failed to exhibit a tremor or a stagger. Any mouse of the boggler strain which appears entirely normal throughout an observation period at the age of 16 months or more, therefore, can be identified as a non-boggler with a fair degree of confidence. Higher accuracy of identification is obtained, of course, if the number of tests is increased or if the mice are observed when they are older.

The bogglers which had convulsions in the absence of a sound stimulus developed a tremor and stagger at a relatively early age. Among nine convulsive bogglers which were tested before they were 11 months old, seven were identified as bogglers at five, seven, seven, eight, eight, nine, and 10 months of age, respectively. These seven expressed the boggler character clearly during the first test given them after they were more than four months old. The other two mice of the group were not identified as bogglers until they were more than 10 months old, but they did show a mild stagger at nine and 10 months, respectively. In contrast to the convulsive bogglers, the few hairless bogglers which have been raised were uniformly late in exhibiting a tremor or an abnormal gait. Five of them were tested when they were from 10 to 12 months old, but the earliest age at which any of them exhibited the boggler character clearly was 13 months. Observations such as these suggest that the recessive gene for hairlessness interferes with the expression of the boggler character and that susceptibility to convulsions either enhances boggling or is a part of the boggler syndrome which becomes apparent only when the other symptoms are unusually severe. Additional data, however, are needed before the relationship of hairlessness and convulsive tendency to boggler can be assessed.

Even among bogglers which were not hairless and which were not observed to be convulsive, the range in the age at which a tremor or a stagger could first be recognized extends from three to 16 months. No differences in grade of boggling which were significant and which were also consistently in the same direction in the several age classes were found between brown-tip bogglers and ones having the alternative pelage character black-tip, between males and females, or between bogglers which were subspecific hybrids and ones which belonged to the subspecies P. m. blandus.

Variability among Nonbogglers

An estimate of the proportion of times that boggling is simulated by normal animals is provided by the behavior of members of the F_1 generation, all of which, if boggler is a completely recessive character (see Inheritance), are expected to be nonbogglers. Thirteen mice of the F_1 generation from crosses between affected individuals of the boggler strain and animals with normal-behavior patterns from the yellow and hairless strains were tested a total of 54 times when they were more than 15 months old. Ratings of behavior were "normal" for 50 of these observations, "probably abnormal" for two of them, and "abnormal" for the remaining two trials. Provided that the likelihood of a display of abnormal behavior does not vary among individuals within the F_1 generation and that it is unaffected by age, each of the 54 tests can be considered to have equal value. The estimated proportion of tests, therefore, during which nonbogglers will seem abnormal is .04 ± .03.

Because this estimate is based upon the behavior of mice of the F_1 generation, it only applies strictly to heterozygotes. In no heterozygote, however, has the behavior been found thus far to be clearly differentiable from that of homozygous normal animals. Therefore, the estimate, although derived from an F_1 generation, may be used with a fair amount of confidence to predict behavior of homozygous nonbogglers as well as that of heterozygotes. An identification of boggler on the basis of a single test during which a tremor or stagger is clearly displayed has a good chance of being correct. If a sufficient number of tests are given, the mice which are not consistent in their behavior can be identified by the proportion of tests during which they were rated abnormal.

Criteria for the Classification of Bogglers and Nonbogglers

Because symptoms of the boggler character were first expressed clearly in some affected individuals at 16 months, no mice have been classified as nonbogglers unless they were tested at least once after they attained this age. Animals which have never been rated either "abnormal" or "probably abnormal" were classified as nonbogglers, if they had been tested at least once after they were 16 months old. The mice which were rated probably abnormal or abnormal during one or two tests, but normal during at least three-fourths of the tests given them when they were more than 15 months old are also classed as nonbogglers, if they were normal during their last test and if they were observed at least four times when they were more than 15 months old and at least once when they were more than 18 months old. In such instances the earlier classification of abnormal was assumed to be an error.

Mice which showed during any test either a tremor or a staggering gait to a degree that seemed unmistakably abnormal have been classified as bogglers, unless their behavior has been normal during at least half of the tests after they were 16 months old. A few individuals which were tested only twice after they reached 16 months of age could not be classified.

Objectivity of the identifications was checked by comparing the ratings of different observers. Forty-seven mice which I classified as bogglers were tested when they were at least 16 months old by from one to three other observers. Two of the 47 were rated probably abnormal by one of the other observers and abnormal by another. There was complete agreement concerning the classification of the remaining 45 animals as bogglers. Furthermore, both a tremor and a stagger were noted by the other observers in all but four of the 47 mice.

There was more variability among observers in the grading of 49 mice which I had identified as nonbogglers. The combined ratings of the three other graders provide the following identifications for these animals: 25 normal, 17 probably abnormal, and seven abnormal. Although seven of the 49 mice were rated abnormal for one symptom on at least one test, none was ever seen to express both a tremor and a stagger to a degree which seemed certainly abnormal, and none, when tested more than once by the other observers, was found to be consistently abnormal. None of the 49 mice, therefore, seemed as abnormal to any observer as did the great majority of the 47 animals which were classified as bogglers. Even though the different observers used somewhat different criteria for rating behavior, there was general agreement in the relative limits of the two groups.

FERTILITY AND VIABILITY

Bogglers may retain the power to reproduce for many months after they first exhibit a tremor and a stagger clearly. Twenty-four female bogglers and 19 male bogglers were known to have become parents in the laboratory and some of their offspring in turn have reproduced. The ages, to the nearest month, of affected parents when their last litters were born varied from 11 to 30 months among females and from seven to 44 months among males. Eleven each of female and male bogglers were more than 24 months old at the time of birth of their last litters.

Data are insufficient to detect small differences in viability which may exist between bogglers and nonbogglers. Insofar as can be determined from the records available, the ability to survive in the laboratory appears to be about equal for the two phenotypes, at least up to 16 months, the age at which classification can be made. Losses from death and escape were high in the boggler strain. Only slightly more than half of the mice which lived long enough to be separated from their parents survived to be classified. The distribution of affected and normal animals among the survivors in segregating generations gives no indication that the losses were preferential for either phenotype (Table III). Of the mice which were lost before they reached 16 months of age, the proportion identified as bogglers is about what would be expected, if allowance is made for the low frequency of expression of the character at early ages. No heterogeneity among types of mating with respect to the proportion of offspring which survived to be tested at 16 months can be demonstrated.

Attempts to keep mice of the boggler strain for as long as three years have been somewhat less successful for affected than for normal animals. But it is not certain that the slightly reduced longevity of these bogglers was a consequence of the gene which determines the boggler character. A few affected individuals lived to an age of more than four years. Since no attempt has been made to rear bogglers under natural conditions, the degree of success that they might have in the wild can be only a matter of conjecture. The boggler character appears to be very ill-adaptive. Mice which stagger and tremble would almost certainly be more vulnerable than normal animals to predators and probably would also be handicapped in their search for food, mates, and homesites. No beneficial effects of the boggler character suggest themselves. Litter size is not observably higher among affected than among normal mice.

Because of the late appearance of their symptoms, however, bogglers may often be successful in transmitting their genes to following generations. The age at which the boggler character is first clearly expressed is rarely as early as three months and may be as late as 16 months. In the prairie deermouse under natural conditions the time of year at which an animal is born greatly affects the age at which its reproductive period begins (Howard, 1949), but a considerable proportion of both sexes of mice of the species P. maniculatus reach maturity, in the field as well as in the laboratory, before three months (Sumner, 1932; Clark, 1938; Blair, 1940; Howard, 1949; McCabe and Blanchard, 1950). Both in the field (Howard, 1949) and in the laboratory (Clark, 1938) females of the species P. maniculatus have borne litters at ages of less than 60 days. By the time they reach three months, some females will already have raised one litter of young. Because reproduction may take place before expression of the character, the boggler gene, unless it produces some as yet unknown deleterious effect in younger life, will be sheltered to some extent against the forces of natural selection.

Onset of the tremor and stagger is not sufficiently delayed to assure complete protection of the boggler gene. In early spring a population of prairie deermice may consist entirely of animals which are at least five months old (Howard, 1949). At this age the abnormality of some bogglers is clearly apparent. Although under natural conditions more than 90 per cent of prairie deermice die before they attain the age of eight months (Howard, 1949), and the majority of deermice die before 12 months (Blair, 1940, 1941, 1948; Howard, 1949; McCabe and Blanchard, 1950), a few are known to have produced litters in the wild when more than 75 weeks old (Howard, 1949). By this age all bogglers would have developed a tremor and stagger. Unless heterozygotes for boggler have an unsuspected advantage over normal homozygotes, the boggler gene in nature may be assumed to be at some disadvantage as compared to its normal allele. The degree of adverse selection, however, probably is reduced substantially by the late appearance of the gene's manifestations.

INHERITANCE

Bogglers were outcrossed to nonbogglers of two strains. Outcross I consisted of one mating of a boggler male with a yellow nonboggler female. Outcross II consisted of two matings of boggler females with two hairless nonboggler males. An F_1 and an F_2 generation were raised from each outcross. Seven mice which could be identified as heterozygotes without a progeny test were mated back to bogglers. One of the heterozygotes used belonged to the F_1 generation from outcross I. The others were mice which had developed neither a tremor or a stagger by the age of 20 months and which had one affected parent and one phenotypically normal parent from the boggler strain.

The three boggler parents of the F_1 generation were brown-tip animals of the subspecies P. m. blandus. The bogglers which were mated with heterozygotes and with other bogglers included both brown-tip blandus and also subspecific hybrids from one or the other of the outcrosses. Some of them came from matings of boggler x boggler, others had only one affected parent, and still others had only phenotypically normal parents.

The yellow mouse and the two hairless animals which were mated with bogglers had behaved normally when they were examined at 28, 20, and eight months of age. In fact, no behavior resembling boggling has ever been observed in any individual of either the yellow or the hairless strain. The mice of the F_1 generation from outcross I which were used in matings include three untested individuals and one which we could not classify, although it was checked twice when more than 15 months old. All the other mated animals of the F_1 generation were identified as nonbogglers.

The distribution of bogglers and nonbogglers in the F_1 and F_2 generations, and among the offspring from matings of boggler x heterozygote, and boggler x boggler is presented in Table III. Except for a few that were discarded before they reached the age of 16 months, offspring are included in the table only if they lived long enough to be tested after they were 16 months old. Of the 70 nonbogglers all but 12 were observed more than once after they attained 16 months of age and all but four were at least 17 months old when last tested. Of the 82 bogglers all but 13 expressed the character plainly on more than one test and all but three were observed to exhibit both a tremor and a stagger. All the mice were tested thoroughly enough at sufficiently advanced ages to make the proportion of misidentifications negligible.

The two sources of possible bias in the observed distributions of the

TABLE III

Frequency Distribution of Nonbogglers and Bogglers among Offspring from Four Types of Mating

Bg Bg = homozygous nonboggler; Bg bg = heterozygote; bg bg = boggler

Type of Mating	No. of Sibships	Offspring					Ratio of Nonbogglers : Bogglers	
		Tested at 16 Months of Age or More			Discarded before 16 Months	Total	Observed (Omitting the Unclassified and Discarded Animals)	Expected
		Nonbogglers	Bogglers	Unclassified				
Bg Bg x bg bg								
Outcross I . . .	1	4	0	1	2	7	All nonbogglers	All nonbogglers
Outcross II . .	2	8	0	0	0	8		
Total F_1	3	12	0	1	2	15		
Bg bg x Bg bg								
Outcross I . . .	3	4	3	0	2	9		
Outcross II . .	2	35	13	0	0	48		
Total F_2	5	39	16	0	2	57	2.44 : 1	3 : 1
Bg bg x bg bg . . .	7	19	20	3	2	44	0.95 : 1	1 : 1
bg bg x bg bg . . .	12	0	46	0	2	48	All bogglers	All bogglers

mice which were classified are (1) the failure to achieve complete classification and (2) the disposal of a few animals for unrecorded reasons before they reached 16 months of age. None of the discarded or unclassified individuals, however, exhibited behavior which was completely unexpected, and their numbers are so few that their exclusion from the data cannot introduce sufficient bias to alter the main conclusion. In the F_1 generation the two discarded mice from outcross I, as expected, displayed only normal behavior whenever they were tested. The one unclassified individual of this generation and outcross appeared abnormal on its last test at 35 months of age, although it had seemed normal only five months earlier. Its behavior on its last test was unlike that usually displayed by nonbogglers but may have been a simulation of boggling, such as has been recorded occasionally for mice which seemed certainly to be nonbogglers. Neither of the two discarded offspring from matings of boggler x boggler displayed either a tremor or a stagger, but this failure to express the characteristic symptoms may be explained by the fact that they were so young, only one and four months old, respectively, when last tested.

TABLE IV

Chi-square Tests for Segregation of Boggler

Mating	Expected Ratio of Nonbogglers : Bogglers	Degrees of Freedom	Observed Distribution among Classified Mice		Hypothetical Distribution if Unclassified and Discarded Mice are included in the Boggler Class	
			χ^2	Probability	χ^2	Probability
Bg bg x Bg bg	3 : 1	1	0.491	.50 - .30	1.316	.30 - .20
Bg bg x bg bg	1 : 1	1	0.026	.90 - .80	0.818	.50 - .30

In order to gauge the extent of bias which the exclusion of the unclassified and discarded animals might introduce into the data for the F_2 generation and the sibships from matings of heterozygotes x bogglers, chi-square tests of goodness of fit were made. They were made both for the observed distributions of the classified animals and for the hypothetical distributions having the greatest deviation from expectation which might have been obtained, if no mice had been discarded and if all the survivors had been classified (Table IV). The mice which were classified included slightly more than the expected proportion of bogglers. But even when the boggler class was increased by the number of all the discarded animals and all the unclassified individuals among mice tested when they were at least 16 months old, the deviation from expectation was not significant.

For the mice which were classified the distribution is in complete agreement with the hypothesis that the boggler character is determined by a single pair of autosomal recessive genes, that the penetrance of the boggler gene is high and perhaps complete, and that bogglers and nonbogglers are about equally viable (Tables III and IV). In the F_1 generation of the outcrosses all 12 of the classified mice were nonbogglers. From matings of boggler x boggler all 46 offspring which were tested when at least 16 months old gave clear exhibitions of the boggler symptoms. Since no heterogeneity between the F_2 generations from the two outcrosses can be demonstrated (exact probability = .40), the test for goodness of fit was made on the combined data from both outcrosses. The distribution of 39 nonbogglers to 16 bogglers is very close to the expected 3:1 ratio. Among offspring from matings of heterozygotes to bogglers the distribution of 19 nonbogglers and 20 bogglers is as close a fit to the expected 1:1 ratio as can be realized with an uneven number of animals.

The evidence is conclusive that boggler is a unit-gene character, but whether it is completely recessive is less certain. The seemingly abnormal behavior of the one mouse of the F_1 generation at 35 months of age may have been, as I suggested, a rare simulation of boggling by a normal animal. An alternative explanation is that a heterozygote for boggler may develop the character when it becomes very old. The ratings of abnormal and probably abnormal given 24 of 49 nonbogglers by observers other than myself, may indicate that the boggler gene has a slight effect in heterozygotes. This possibility has not been thoroughly explored. This much can be said, however, expression of the boggler character in heterozygotes, if present at all, only occurs at an extremely late age or is so weak that more delicate tests than these are necessary to distinguish between heterozygotes and homozygous normal animals. Among 12 mice of the F_1 generation of the outcrosses which were classified as nonbogglers, nine individuals were tested at least once when they were more than 30 months old, and three were observed when they were more than 40 months of age. With the genetic background provided by the boggler strain, heterozygotes certainly cannot be distinguished from normal homozygotes during the first two years of life by the methods of observation which have been used in this study. Hence, I consider the gene for the boggler character to be recessive and propose the symbol bg for it.

LINKAGE TESTS WITH HAIRLESS AND WITH BROWN-TIP

A small amount of information pertinent to the linkage relations between boggler (bg bg) and the characters hairless (hr hr) and brown-tip (bb) was collected incidental to the study of the inheritance of boggler. The F_2 generation of the cross between haired bogglers and hairless nonbogglers constitutes a linkage test in the repulsion phase for hairless vs. boggler (Table V). Because all three of the bogglers which entered the outcrosses were brown-tipped (bb bg bg), whereas their mates, both yellow and hairless ones, were homozygous for the alternative dominant pelage character black-tip (BB Bg Bg), the F_2 generations from both outcrosses provide a linkage test in the coupling phase for brown-tip vs. boggler (Table VI). The discrepancy between the total shown in Table VI and that for the F_2 generation in Table III results from the fact that the hairless segregants could not be included in the linkage test because they were not checked before they lost their fur and consequently their pelage color could not be determined. The data have been analyzed by the procedures set forth by Mather (1951). Estimates of recombination fractions and their standard errors have been calculated by Fisher's scoring method (Fisher, 1946; Mather, 1951).

TABLE V

Tests for Linkage between Hairless and Boggler

F_2 Repulsion
Hr bg/hr Bg x Hr bg/hr Bg

Class	Observed	Expected
Haired nonbogglers	30	27
Hairless nonbogglers	5	9
Haired bogglers	11	9
Hairless bogglers.	2	3
Total	48	48

Analysis of Chi-square

Source of Variation	Degrees of Freedom	χ^2	Probability
Haired : hairless segregation . . .	1	2.778	.10 - .05
Nonboggler : boggler segregation . .	1	0.111	.80 - .70
Independent assortment.	1	0.000	1.00
Total.	3	2.889	.50 - .30

Estimation of Recombination Fraction
by Fisher's Scoring Method

Recombination Fraction p	Score	Information	Standard Error s_p	5 Per cent Fiducial Limits $p \pm 2.012\ s_p$
.50	0.0000	85.3333	.108	.28 - .72

The single-factor ratios are in good agreement with expectation and no evidence of linkage between either of the two pairs of characters was found. Both in the test of hairless vs. boggler and in the test of brown-tip vs. boggler the chi-square for independent assortment is zero (probability = 1.0) and the estimate of the recombination fraction and its standard error is .500 ± .108. The lower fiducial limit for the recombination fraction, at the 5 per cent level of significance. is .28 (p - 2.012 s_p, where p is the observed recombination fraction and s_p is the standard error of that fraction). Boggler is therefore demonstrated not to be tightly linked to either hairless or brown-tip and it may segregate independently from both of these characters. The tests, however, are not adequate to exclude the possibility that one or both pairs of characters are loosely linked with a recombination fraction of more than 27 per cent.

TABLE VI

Test for Linkage between Brown-tip and Boggler

F_2 Coupling
b bg/ B Bg x b bg/ B Bg

Class	Observed	Expected
Black-tip nonbogglers	24	27
Brown-tip nonbogglers	10	9
Black-tip bogglers	10	9
Brown-tip bogglers	4	3
Total	48	48

Analysis of Chi-square

Source of Variation	Degrees of Freedom	χ^2	Probability
Black-tip : brown-tip segregation	1	0.444	.70 - .50
Nonboggler : boggler segregation	1	0.444	.70 - .50
Independent assortment	1	0.000	1.00
Total	3	0.888	.90 - .80

Estimation of Recombination Fraction

by Fisher's Scoring Method

Recombination Fraction p	Score	Information	Standard Error s_p	5 Per cent Fiducial Limits p ± 2.012 s_p
.50	0.0000	85.3333	.108	.28 - .72

COMPARISON WITH OTHER INHERITED ABNORMALITIES OF BEHAVIOR

Of the observed abnormalities of behavior in the genus Peromyscus the one which most closely resembles boggler is a recessive tremor and shambling gait which has appeared among hybrids between P. m. gambeli and P. m. rubidus (Huestis and Barto, 1936). In both this character and boggler the tremor affects body and limbs and its severity increases with age. But the tremor in the gambeli-rubidus hybrids can be noted when the animals are moving and it is clearly more pronounced during activity than during rest. This is not true in boggler, in which the tremor is usually apparent only when the affected individual is inactive. The display of symptoms at two weeks of age by the affected gambeli-rubidus hybrids, their stunted growth, and their death at five weeks or less further distinguish them from bogglers. Inasmuch as the syndromes in the two strains differ in many respects, it seems highly probable that the genes which determine the two characters are different. Because the tremor strain is now extinct, breeding tests for genetic identity of the two characters are not possible.

In the house mouse several characters are known which involve a gait somewhat like that of bogglers. In one of these disorders the syndrome includes both a tremor and convulsions; in others a tremor is present but convulsions are not; in still others convulsions occur but a tremor is absent; and in one, abnormality of gait is the only symptom. Two of the genes which affect gait also affect pelage color. In the genetic backgrounds in which the boggler gene has been carried it has not been observed to influence pigmentation. Its relationship to convulsive tendency is obscure. Until this relationship is known, the full extent of the similarity or dissimilarity between the symptoms of boggler and those of any other character cannot be judged. The abnormalities of the house mouse which have been described fully differ in important particulars from boggler. One, trembler (Falconer, 1951), is characterized by convulsions, spastic paralysis which involves the hind limbs to a greater extent than the front limbs, and a tremor which, unlike that in boggler, is exhibited only when the mouse is active. The trembler syndrome is further unlike the boggler in that some of its symptoms become less pronounced with advancing age. Among tremblers convulsions are frequent only in young animals and the paralysis, which makes its appearance before the tremor, becomes less severe as the mice get older. In bogglers tremor and staggering gait are recognizable at about the same time, and both symptoms become steadily worse with increasing age.

Characters of the house mouse, in which an abnormal gait and a tremor but not convulsions are found, are reeler (Falconer, 1951), wabbler lethal (Dickie, Schneider, and Harman, 1952), and agitans (Hoecker, Martinez, Markovic, and Pizzaro, 1954). The tremor in all three of these characters is most pronounced when the animal is moving. In reelers, the hind quarters sway from side to side even when the affected mice are standing still; the gait, unlike that of bogglers, improves with age. Furthermore, the inactivity, lack of aggressiveness, and unkempt appearance of reelers find no parallel in the boggler syndrome. Mice with the wabbler lethal character walk with the body close to the ground, whereas at least in some bogglers, the hind quarters often appear to be elevated more than in normal animals. Other symptoms of wabbler lethal, not shared by bogglers, are the failure to react to a pinch on the tail and a locking of the hind feet together when the mouse is suspended by the tail. Agitans mice have a rapid, stiff-legged gait when they are young which later changes to a waddle. Reduction in muscular tone, inability to swim, and crossing the hind legs when the animal is lifted by the tail are symptoms of agitans but not of boggler.

Characters of the house mouse which include an abnormal gait and convulsions but not a fine tremor are jittery (DeOme, 1945), dilute lethal (Russell, 1951; Searle, 1952), and varitint waddler (Cloudman and Bunker, 1945). Neither jittery nor dilute lethal mice exhibit any kind of tremor. Varitint waddlers lack a tremor comparable to that of bogglers but they do exhibit choreic head movements. The dilute lethal gene has the same effect on pigmentation of the fur as its allele dilute, and the varitint-waddler gene produces extensive spotting. Additional symptoms of varitint-waddler are running in circles and deafness. A character in the house mouse which has a gait similar to that of boggler but neither a tremor nor convulsions is ducky (Snell, 1955). Toeing out of the hind feet is a symptom of both ducky and boggler and in both a reeling gait develops which becomes progressively worse with age.

The genes reeler, agitans, jittery, dilute lethal, and ducky, like boggler, are recessive; wabbler lethal and varitint waddler are incompletely dominant; and trembler is completely dominant. All of these disorders differ from boggler in that they make their appearance at an early age and are characterized by lowered viability of young animals. Ducky, which has the latest age of onset of any of these eight characters in the house mouse, can be classified with certainty at 40 days, whereas the earliest exhibition of boggler so far observed was 87 days, and a few bogglers were not clearly abnormal until 16 months. None of the jittery or dilute lethal mice and none of the homozygous wabbler lethal mice live to reproductive age. In the other six characters some individuals reach maturity, but sterility is high in one or both sexes among the survivors.

To the list of characters in the house mouse which are similar to boggler in having an abnormal gait should be added one other: ataxia (Carter and Phillips, 1952). Because this disorder has not been described, the closeness of the resemblance to boggler is not known.

SUMMARY

Boggler, an inherited abnormality of the deermouse, was discovered in a laboratory stock of Peromyscus maniculatus blandus which was descended from mice trapped near Tularosa, New Mexico. The ancestry of all bogglers traces back through both parents to a pair of mice in the first cage-bred generation of this stock. The mutation to boggler must have occurred no later than the first cage-bred generation and probably had its origin in the wild population.

Manifestations of the boggler character which are regularly expressed are (1) a fine tremor which usually is apparent only when the mouse is at rest and awake and (2) in-co-ordinate movements of the hind

limbs which result in a staggering gait. The front limbs appear to move normally. Attempts to separate tremor and staggering gait by outcrossing were unsuccessful. Both symptoms, therefore, are considered to be manifestations of the same gene. There is a suggestion, but not proof, that proneness to convulsions also may be part of the boggler syndrome.

The age at which the tremor and stagger are first expressed clearly is as early as three months in some individuals and as late as 16 months in others. Although most of the affected mice which were tested at eight months exhibited boggling occasionally, a single observation at that age revealed clearly abnormal behavior in only about half of them. After the symptoms make their appearance they become progressively worse with age.

Under laboratory conditions the viability of bogglers is about equal to that of normal animals of the boggler strain, at least up to the age of 16 months. Affected individuals have lived to be more than four years old.

Bogglers of both sexes are fertile. Inasmuch as the reproductive period of peromyscus in nature often begins well before the age at which boggling becomes apparent, the boggler gene may be assumed to be protected to some extent from adverse natural selection by the delay in the manifestation of its effects.

The gene for boggler (bg) is an autosomal recessive. Its penetrance is high and perhaps complete.

No evidence of linkage was found between boggler and either browntip or hairless, but loose linkage, with more than 27 per cent crossing over, is not disproved.

The boggler syndrome differs from that of any other abnormality which has been described for mice of the genera Peromyscus and Mus.

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